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IS A *DE NOVO* PROTEIN SYNTHESIS A REQUISITE FOR A DEVELOPMENT OF A COMPLETE FEBRILE RESPONSE TO CYTOKINES IN MAMMALS ?

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Anisomycin (ANI), a relatively non-toxic protein synthesis inhibitor, supresses fevers normally evoked by endotoxin or crude endogenous pyrogen (EP). The purpose of this study was to determine the role of protein synthesis on fevers evoked by human recombinant interleukin-1ß (hrIL-1ß), macrophage inflammatory protein-I (MIP-1), and prostaglandin E_2 (PGE_2). Stainless steel guide cannulae were implanted stereotaxically above the lateral cerebral ventricle (LCV) or above both the anterior hypothalamic preoptic area (AH/POA) and third cerebral ventricle in two groups of rats. In Long Evans rats, hrIL-1ß and PGE_2 infused into the LCV induced characteristic fevers. The febrile response to hrIL-1ß (100ng/10μl) was suppressed by ANI (80μg/10μl) infused into LCV 30 min before administration of the pyrogen. Analogous pretreatment with ANI had no effect on the initial pyrexia evoked by PGE_2 (250 ng/10 μl). Although, in contrast, ANI infused at the same dose into the third cerebral ventricle significantly diminished the febrile response to PGE_2 (100ng/1μl) micro-injected into the AH/POA. A novel immunoneuromodulator and pyrogen, MIP-1, when applied to the cells of AH/POA in Sprague Dawley rats evokes an intense fever which is not blocked by prostaglandin synthesis inhibitors. Infusion of ANI (80μg/10μl) into the third cerebral ventricle before the bilateral micro-injection of MIP-1 (14pg/0.5μl) into AH/POA significantly attenuated the rise in colonic temperature for 1.0 to 3.0 hrs. These results are supported by findings showing that a *de novo* protein synthesis occuring between the production of EP and the final cellular responses in the CNS leading to fever is necessary for the development of a complete febrile response. [Supported in part by NIH NS26045 to W.D.R., Sigma Xi Research Award to W.M.Z., and NSF IBN-91-21656 to R.D.M.]